Case Report

Pseudopterygium: Unique Conjunctival Stricture Observed in Japanese White Rabbit

Osamu Katsuta¹, Katsuhiko Shinomiya¹, Takaharu Mochizuki¹, Chinami Kikkawa¹, Miwa Yoshimi¹, and Toshimi Ikuse¹

¹Drug Safety and Pathology Group, Research & Development Center, Santen Pharmaceutical Co., Ltd., 8916–16 Takayama-cho, Ikoma-shi, Nara 630–0101, Japan

Abstract: A unique conjunctive stricture was observed in the eye of a male 17-week-old Japanese White rabbit (Kbl:JW). The conjunctival membrane had proliferated centripetally and covered a large portion of the cornea. However, the membrane did not adhere to the cornea. Histopathologically, the inner epithelium of the conjunctival membrane appeared flattened, while the outer epithelium had become stratified and squamous. Goblet cells were observed on both sides of the epithelium. The lamina propria consisted of well-developed, vascularized collagen fiber. Myxoid change was seen near the tip of the membrane. In animals, these conjunctival membranes have been reported in a few dwarf rabbits, dogs and horses and have had various different terms applied to them due to their unknown etiology. Based on the conventions of human ophthalmology, such lesions should be regarded as pseudopterygia. Therefore, the present case was diagnosed as involving a pseudopterygium. The centripetal proliferation of the conjunctival membrane may be a characteristic finding in animal cases. Our goal is to encourage accumulation of such cases by researchers and practitioners working in the field of toxicology. (J Toxicol Pathol 2008; 21: 239–241)

Key words: conjunctive stricture, pseudopterygium, rabbit, animal ophthalmology

Pterygia and pseudopterygia are well-known conditions in human ophthalmology^{1,2}. Meaning *small wing* in Greek, a *pterygium* refers to a raised triangular growth on the corneal limbus, with an apex or head located on the cornea. Such growths tend to be oriented laterally in the interpalpebral fissure on either the nasal or temporal side of the cornea and adhering to the corneal epithelium¹. In contrast, a pseudopterygium can arise anywhere around the bulbar conjunctiva, with no corneal adhesion, and can lead to scarring of the conjunctiva. Reportedly, pseudopterygia tend to emerge following chemical injury, corneal ulcerations or other inflammatory problems².

While pterygia/pseudopterygia are rarely observed in animals, pseudopterygium-like disorders have been reported in pet Dwarf^{3–5}, Pygmy⁶ and Rex⁷ rabbits. In animals, these lesions tend to assume a unique configuration, wherein the cornea is progressively covered by hyperplastic conjunctiva around the entire perimeter. Since the etiology is currently unknown, these growths/lesions are referred to using various different terms, including conjunctival strictures,

pseudopterygia, conjunctival centripetalization, precorneal or epicorneal membranous occlusions, circumferential conjunctival hyperplasia and placation and conjunctival hyperplasia^{5,8}.

In a toxicological study, we recently encountered a rabbit with a lesion consistent with the characteristics of pseudopterygia. Herein, we describe the macroscopic and microscopic characteristics of the lesion and discuss nomenclatural issues.

A male, 8-week-old Japanese White rabbit (Kbl: JW, SPF), was one of 28 animals purchased from Kitayama Labes Co., Ltd. (Nagano, Japan). These rabbits were individually housed in stainless steel cages (489 mm wide × 588 mm high × 363 mm deep; Kears Co., Ltd., Wakayama, Japan) maintained in a climate-controlled animal room (temperatures ranging between 19°C and 25°C and relative humidity ranging between 30% and 70%) with a 12-hour light/dark cycle, and were given *ad libitum* access by an automated system to tap water and a gamma-ray sterilized pellet diet of approximately 130 g/day (LRC4; Oriental Yeast Co., Ltd., Tokyo, Japan). The treatment and handling of animals were approved by the Animal Care and Use Committee of the Nara Research & Development Center, Santen Pharmaceutical Co., Ltd.

The rabbit in question was initially used in an eye irritation study in which the right eye was treated with a test compound while the left eye was kept untreated. While no

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Mailing address: Osamu Katsuta, Drug Safety and Pathology Group, Research & Development Center, Santen Pharmaceutical Co., Ltd., 8916–16 Takayama-cho, Ikoma-shi, Nara 630–0101, Japan
TEL: 81-743-79-4509 FAX: 81-743-79-4591
E-mail: osamu.katsuta@santen.co.jp

Fig. 1. Macroscopic appearance of the left eye. The bulbar conjunctival membrane concentrically covers the cornea, with marked vascularization.

Fig. 2. Low magnification view of the left eye. The conjunctival fold protrudes centrally from the corneal limbus along the surface. U, upper fold; L, lower fold. HE stain. $\times 3.7$.

Fig. 3. Higher magnification of the upper fold. The inner epithelium of the fold and the regional corneal epithelium are flattened. The tip of the fold becomes a thick stratified squamous epithelium that compresses the corneal epithelium. HE stain. $\times 100$.

Fig. 4. The lower fold and cornea. The regional corneal epithelium is elongated into a single layer, and the margin assumes a pyramidal form due to compression. Watanabe's silver impregnation stain. $\times 100$.

Fig. 5. The lower fold. The stroma consists of well-developed collagen fiber. Masson's trichrome stain. $\times 200$.

Fig. 6. The lower fold. Near the tip of the fold, the stroma undergoes a myxoid change, possibly due to mechanical pressure. AB-PAS stain. $\times 200$.

abnormality was observed in either eye four weeks after the study ended, the rabbit was observed to bump its head against the cage walls from time to time. Five weeks later, an overgrowth of the conjunctiva was found on the left eye, the eye left untreated in the preceding study. The overgrowth of conjunctival tissue consisted of an opaque, congested mass concentrically covering the cornea. No discharge was associated with this overgrowth (Fig. 1). The field of vision remained unimpaired, as the pupil had yet to be covered by the overgrowth. The conjunctival overgrowth did not adhere to and was easily separated from the cornea.

During the subsequent week, the rabbit was euthanized by exsanguination under deep anesthesia achieved by intravenous injection of sodium pentobarbital. Necropsy showed no abnormal findings, except in the left eye. The upper and lower palpebrae, nictitating membranes, Harderian glands, and lacrimal glands were dissected and fixed in 10% neutral buffered formalin (10% NBF). Both eyeballs were immersed overnight in F-G fixative solution (a mixture of 10% neutral buffered formalin and 2.5% glutaraldehyde) and then fixed in 10% NBF. After fixation, the eyeballs were trimmed perpendicularly with the optic nerve still attached. All preserved tissue was embedded in paraffin and sectioned, and the sections were stained with hematoxylin and eosin (HE). Additionally, sections from both eyeballs were stained with Masson's trichrome stain, elastic van Gieson (EVG) stain, alcian blue (AB) stain with periodic acid-Schiff (PAS) reaction, Gram stain and Watanabe's reticulin silver impregnation.

Microscopic observation showed that the club-shaped conjunctival fold protruded centrically from the corneal limbus along the corneal surface (Fig. 2). The corneal aspect of the fold was covered by flattened epithelium, and the free aspect was covered by a stratified cuboidal or thin squamous epithelium. Goblet cells were widely scattered among the epithelia of both aspects. At the tip of the fold, the epithelium turned into a metaplastic nonkeratinized stratified squamous epithelium (Fig. 3). The corneal epithelium was elongated and flattened at the site covered by the fold, whereas the epithelial layer had thickened, becoming pyramidal where it approached the edge of the fold (Fig. 4). The collagen fibers were well-developed, and capillaries of varying sizes were found in the stroma (Fig. 5). EVG staining showed no arteries or arterioles. A few lymphocytes, plasma cells and heterophils were found scattered within the epithelium and connective tissue. However, Gram staining showed no bacteria. Myxoid foci appeared near the tip of the fold in the AB-PAS staining (Fig. 6). This lesion was likely attributable to the physical pressure of blinking. The corneal stroma exhibited slight edematous swelling in the region covered by the fold. No abnormalities were found in the nictitating membrane, palpebrae, Harderian gland or lacrimal gland of the left eye. The right eye and associated apparatus were intact.

Disorders like the one described in the present case have been reported in some pet Dwarf³⁻⁵ rabbits. The same condition has also been described among dogs and horses⁹.

Among experimental animals, a New Zealand white rabbit⁹ has been diagnosed with pseudopterygium. Although experimental rabbits are often used in toxicological and ophthalmologic studies in the development of eye drops, cosmetic compounds and other chemicals, there is virtually nothing in the literature, other than a single article⁹, in regard to the centripetal proliferation of the conjunctiva. Our case could also be referred to using other terminology, such as hyperplasia or dysplasia. However, based on the conventions of human ophthalmology^{1,2}, we believe the present case should be regarded as an instance of pseudopterygium, given the observations of conjunctival overgrowth and no adhesion to the cornea. We also wish to propose a nomenclatural convention for wider use of the term *pseudopterygium* in experimental animal studies. Although the etiology of the condition known as pseudopterygium remains unclear, injury or inflammation is believed to be a trigger². In the present case, the rabbit was observed to have the habit of bumping its head against cage walls. This behavior may stress the eye, increasing the risk of trauma.

It remains unknown why the conjunctiva proliferates centripetally, although the centripetal proliferation in affected eyes has been described in the case of dogs⁹. This type of pseudopterygium has not been documented in humans. The difference may ultimately be attributable to interspecies differences. Many more cases are required to examine and clarify this phenomenon.

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